# Preclinical testing and the possible risk of inadvertent germline alteration by somatic cell gene therapy

## March 12, 1999
## RAC

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**CBER, FDA**

# Concern about risk to germline: Changes in gene therapy resulting in evolving policy

**Earlier:**

- **Gene therapy *ex vivo***
- **All for serious or life-threatening conditions**

**More recently:**

- **Many gene therapies *in vivo***
- **Some for mild conditions**

**Future: enhancement?**

# History

**1982** **Splicing Life emphasizes distinction between somatic cell and germ-line therapies**

**1989** **Revised "Points to Consider" of the RAC terms inadvertent germline alteration an undesirable consequence, and requires submission of information in protocols to assess this possibility.**

# Previous RAC consideration

**James Neel, University of Michigan, advisor invited to the RAC, 9/14/92.**

**"…one aspect of somatic cell therapy that should have high priority, namely, meticulous testing for unanticipated germ-line intrusions of the vectored DNA."**

**"While the prospects [of germline alteration]... seem slim, data to this effect are urgently needed."**

**"…efforts to detect gonadal intrusion by foreign DNA should become a standard requirement…"**
**(Hum. Gene Ther. 4:127, 1993)**

# Recent RAC consideration of risk of germline alteration

| | |
|---|---|
| **12/15/97** | **FDA discussion of vector biodistribution to the gonads in some animal studies. RAC decision to request data from PI's and IBC's.** |
| **3/9/98** | **RAC discussion of responses, RFA, sharing of data. Goal: data available to all investigators, database for comparison of vectors and routes.** |
| **1/7/99** | **RAC policy conference on *in utero* gene transfer. Detection and assessment of inadvertent germ-line transmission identified as needing further study.** |

# Inadvertent germline alteration: spectrum of potential risk

**Lowest**

**Intermediate range? Risk unknown and not quantitated**

**Highest**

***Ex vivo* gene therapy**

**Somatic cell therapy**
**Organ and tissue transplants**
**Blood**

***In vivo* gene therapy**

**Plasmids**
**Adenoviruses**
**Retroviruses**
**AAV**
**Other**

**Insertional elements entering the genome:**

**Retrotransposons**

**Note: Teratogenesis a separate concern, not discussed today.**

# The dilemma

- Genetic elements can integrate and alter the germline (retrotransposons, retroviruses)
- Vectors with some capacity to integrate (even plasmids) are used for gene therapy
- Vectors are detected in the gonads
- Data are inadequate to rule out inadvertent germline alteration, to assess whether vector enters germ cells and integrates.

## Germline alteration to be avoided currently

Vector integration into the germline, even without apparent adverse effects, not currently accepted.

- Some possible biological consequences could take decades to appear. For example, could emerge only at puberty, or only during reproduction.

- Even if no biological effect:
  Lack of adequate public debate and societal consensus.

## The practical problem

- Like other risks, risk is not zero but may be very low. What frequency of events would society accept?

- How good, how quantitative must the data be, to permit phase I trials? For later development, wider use? Note: data not currently quantitative.

How encourage development of promising therapies, yet satisfy the public that all reasonable efforts are being made to avoid inadvertently altering the germline?

## FDA's current approach

- Preclinical vector localization studies in animals, for vectors to be given directly to patients.
- PCR analysis of gonadal extracts (presence of vector rather than gene expression is the issue)
- If persistent positive signal, then in general limit clinical trials to sterile individuals while further analysis is performed.
- Risk-benefit analysis will be discussed.

# FDA's goals for this meeting

- Discuss publicly the question of potential germline alteration, put the risk in perspective

- Invite discussion of ethical and social issues:
  Risk to non-consenting progeny, to gene pool
  Preserve societal acceptance of somatic cell gene therapy

## FDA's goals for this meeting, cont'd

- Analyze scientific and technical issues

- Discuss whether FDA's approach is appropriate (nature and stringency of preclinical testing, decisions about clinical trials).

  Are there any gene therapies:
  For which testing need not be completed preclinically? For which + signals in the gonads, without further data, do not preclude clinical trials in fertile individuals?

# Factors in risk assessment

Do any of these factors affect decisions about data needed and clinical trials?

- Non-sterile patient populations for whom reproduction is unlikely: disease state, age, birth control
- Possible future indications, including enhancement
- Patient developmental stage (*in utero*, child, adult)
- Potential for integration of vector class
- Vector formulation
- Route of administration
- Prior experience with similar vector; how similar?

## To be presented:

Dr. Haig Kazazian, Jr. Retrotransposons, example of insertional elements altering human genome

Dr. Lonnie Russell Male reproductive biology

(Future topic: Female reproductive biology)

Dr. Nancy King Social and ethical context

## To be presented, cont'd

CBER:

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|---|---|
| Dr. Andra Miller | Case studies |
| Dr. Steven Bauer | Current FDA approach |

Sponsor presentations:

| | |
|---|---|
| Dr. Katherine High | AAV |
| Dr. Christine-Lise Julou | plasmid |
| Dr. Margaret Liu | retrovirus |

Public comment

## Abbreviated form of questions for the RAC to address:

For gene therapy:

1. Are vector biodistribution studies needed prior to phase I human trials, to see if vector is found in the gonads?

2. Are FDA's current technical recommendations appropriate?

3. If vector is detected transiently or persistently in the gonads and it is not yet known whether it is in germ cells, what should the consequences be for clinical trials?